Digestive and Liver Disease 44 (2012) 185–194

Contents lists available at SciVerse ScienceDirect

Digestive and Liver Disease

journal homepage: www.elsevier.com/locate/dld

Review Article

Diet and risk of inflammatory bowel disease

Vibeke Andersen[a,b,*], Anja Olsen[c], Franck Carbonnel[d], Anne Tjønneland[c], Ulla Vogel[e,f]

[a] Medical Department, Viborg Regional Hospital, Viborg, Denmark
[b] Medical Department, SHS Aabenraa, Aabenraa, Denmark
[c] Danish Cancer Society, Institute of Cancer Epidemiology, Copenhagen, Denmark
[d] Liver and Gastrointestinal Unit, University Hospitals of Paris Sud in Bictre, Assistance Publique Hpitaux de Paris, University Paris Sud, France
[e] National Research Centre for the Working Environment, Copenhagen, Denmark
[f] National Food Institute, Technical University of Denmark, Soborg, Denmark

ARTICLE INFO

Article history:
Received 3 May 2011
Accepted 3 October 2011
Available online 3 November 2011

Keywords:
Animal protein
Crohn's disease
Fish
Food
Intestinal inflammation
Meat
Ulcerative colitis

ABSTRACT

Background: A better understanding of the environmental factors leading to inflammatory bowel disease should help to prevent occurrence of the disease and its relapses.
Aim: To review current knowledge on dietary risk factors for inflammatory bowel disease.
Methods: The PubMed, Medline and Cochrane Library were searched for studies on diet and risk of inflammatory bowel disease.
Results: Established non-diet risk factors include family predisposition, smoking, appendectomy, and antibiotics. Retrospective case–control studies are encumbered with methodological problems. Prospective studies on European cohorts, mainly including middle-aged adults, suggest that a diet high in protein from meat and fish is associated with a higher risk of inflammatory bowel disease. Intake of the n-6 polyunsaturated fatty acid linoleic acid may confer risk of ulcerative colitis, whereas n-3 polyunsaturated fatty acids may be protective. No effect was found of intake of dietary fibres, sugar, macronutrients, total energy, vitamin C, D, E, Carotene, or Retinol (vitamin A) on risk of ulcerative colitis. No prospective data was found on risk related to intake of fruits, vegetables or food microparticles (titanium dioxide and aluminium silicate).
Conclusions: A diet high in protein, particular animal protein, may be associated with increased risk of inflammatory bowel disease and relapses. N-6 polyunsaturated fatty acids may predispose to ulcerative colitis whilst n-3 polyunsaturated fatty acid may protect. These results should be confirmed in other countries and in younger subjects before dietary counselling is recommended in high risk subjects.

1. Introduction

Inflammatory bowel diseases (IBDs) are chronic relapsing inflammatory diseases of the intestinal tract [1,2]. Ulcerative colitis (UC) and Crohn's disease (CD) are the two major phenotypes. The diseases have great impact on the quality of life of the affected persons and their families. They can lead to hospitalizations, surgery, complications and death. The burden on the society is related to disability from disease activity and complications [3,4].

Both genetic and environmental factors contribute to IBD risk. Recently, progress has been achieved in the molecular understanding of the diseases by genetic studies using both candidate genes and genome wide association approaches. These studies have shown that genetic predisposition to IBD involves defects in the epithelial barrier function and in the innate immune system that affect the interaction with commensal bacteria [5–9]. Less progress had been achieved in the identification of environmental factors involved in the development of IBD. The assumption that living conditions and environmental factors contribute significantly to the risk of IBD stems from the dramatic increase in the incidence of IBD in many countries during the recent decades, which is incompatible with a purely genetic disease.

IBD has long been regarded as a result of a dysregulated host microbial interaction in genetically susceptible individuals [10]. Dietary components have been shown to impact gut microbiota, and may additionally affect gut homeostasis directly [11–15]. Thus, a "westernized" diet characterized as low-fibre, high-sugar, high-animal-fat has been proposed to confer susceptibility to IBD [16]. Also, the high response rate in children with CD to exclusive enteral nutrition suggests a major effect of diet on intestinal inflammation [17].

A better understanding of the factors leading to IBD will help prevent disease occurrence and possibly relapses. We therefore

* Corresponding author at: Medical Department, Regional Hospital Viborg, Heibergs Allé 4, DK-8800 Viborg, Denmark. Tel.: +45 8927 2641; fax: +45 8927 3484.
E-mail addresses: vibeke.andersen@viborg.rm.dk, va9791@gmail.com (V. Andersen), anja@cancer.dk (A. Olsen), franck.carbonnel@bct.aphp.fr (F. Carbonnel), annet@cancer.dk (A. Tjønneland), ubv@nrcwe.dk (U. Vogel).

1590-8658/$36.00 © 2011 Editrice Gastroenterologica Italiana S.r.l. Published by Elsevier Ltd. All rights reserved.
doi:10.1016/j.dld.2011.10.001

underwent this study with the aim to critically review the current knowledge on the relation between diet and IBD development.

2. Methods

The PubMed, Medline and Cochrane Library were systematically searched for studies in the scope of diet and risk of IBD (October 2010) using the following terms: diet, nutrients, IBD, CD, UC, aetiology, epidemiology, prospective, case-cohort, case–control, population-based, meat, fibre, fiber, fruit, vegetables, fish, n-3 PUFA, and n-6 PUFA. The terms were used combined and alone and both as MeSH terms and text words. Found articles were scrutinized for references. Selected related articles were also examined.

3. Results

3.1. Epidemiology

Epidemiological studies strongly support an important role for environmental factors in IBD development. The incidence of IBD has increased in Western countries and more recently in Asian countries as these countries became more developed [18,19] and the incidence and prevalence has been found to be higher in developed countries than developing countries [20] (Fig. 1). This suggests that the underlying cause for such a distribution could be westernization, although north-south gradients within Europe [21] and within countries such as Scotland [22], USA [23] and France indicate that development is not the sole determinant [24]. Also data from migration studies indicate that the children take on the risk factors of the new environment whereas the parents maintain their original risk pattern [25].

Family members to an affected index person have a higher risk of IBD compared to the risk of the general population [26]. In UC twins, the concordance ratio of monozygotic vs heterozygotic twins is of 16% vs 4% and in CD twins, the concordance rate is 20–50% in monozygotic vs 10% in heterozygotic twins [27,28]. Although high, these concordance rates are far from 100%.

Taken together, these studies suggest that environmental factors associated with westernized lifestyle are important for IBD development and that the environmental factors have a greater impact on UC than on CD [29].

3.2. Non-diet risk factors

Established risk factors of IBD include smoking [30], appendicitis [31,32], and antibiotics [33]. A meta-analysis showed that current smoking increases the risk of CD with an odds ratio (OR) of 1.76 (95% confidence interval (95%CI): 1.40–2.22) and former smoking increases the risk of UC (OR = 1.79; 95%CI: 1.37–2.34) compared to never smokers. Persons who have had an appendectomy due to appendicitis are less prone to develop UC (standardized incidence ratio 0.45, 95%CI: 0.39–0.53) [32], whereas, on the contrary, a significant risk of CD following an appendectomy has been found (relative risk (RR) of 1.99 (95%CI: 1.66–2.38)) compared to those who have not [34]. Antibiotics have the potential to alter the intestinal microflora. A Nationwide cohort study found that use of antibiotics in childhood was associated with an increased risk of developing IBD with a RR of 1.84 (95%CI: 1.08–3.15) [33]. Gastrointestinal infections have been suggested to confer risk of IBD [35]. Risk of developing IBD was significant higher amongst 13,148 patients exposed to *Salmonella* or *Campylobacter* gastroenteritis than amongst 26,216 control patients [35]. However, detection bias may be involved [36]. Thus, the findings of high incidence rate ratios (IRRs) for IBD the first year after both positive (IRRs 5.4–9.8) and negative (IRRs 53.2–57.5) stool tests suggest increased rates of stool testing of patients with unclear gastrointestinal symptoms might cause detection bias [36].

Solid data supporting the involvement of other factors such as oral contraceptives, education, and socio economic status in IBD development, and a protective effect of being breastfeed for the child are still missing. The hygiene hypothesis is based on the observation that the increased incidence of IBD has coincided with improvements in hygiene. According to this hypothesis, the rise in IBD may be related to limited exposure to microorganisms which are normal stimulants for the maturation towards a balanced immune system. It is not clear if this hypothesis is valid for IBD.

3.3. Gut microbes

Gut microbes are key factors for regulation of the intestinal immune system. Animal studies suggest that colonization by commensal microorganisms is a key to immune development. Recently, the development of molecular tools with a gene marker approach based on the use of bacterial 16S ribosomal RNA has fuelled progress in the understanding of the homeostasis of the gut immune system and gut microbiota in the healthy individual [13,14,37]. Colonization starts at birth and a relatively functionally stable microbiota is achieved at about the age of 2 years [14].

Intestinal microbes are important in IBD development [38]. Animal studies show that IBD does not develop in germ-free conditions [10], but does occur in animals exposed to commensal bacteria [39]. Bacterial diversity of the human gut microbiota in IBD patients has been reported to be low [38], which indicates that the normal balance in the colon might be disturbed and some healthy bacteria are missing or some adverse bacteria have become too dominant [38]. It is, however, not totally clear if this finding is a part of the IBD aetiology or merely a consequence of the disease or its treatment. Studies have shown a decrease in normal dominant bacteria such as *Clostridium leptum* group of the Firmicutes phylum family and the *Faecalibacterium prausnitzii* in CD and UC [14]. The human commensal, *F. prausnitzii* and *Bacteroides fragilis* has been shown to possess anti-inflammatory properties in cell systems and animal models [14,38,40]. Moreover, potentially pro-inflammatory microbes such as entero-adherent and invasive *Escherichia coli* have been found more often in IBD than from healthy individuals [14,38]. Also interestingly, a North to South gradient in the faecal microbiota composition of 6-week-old infants has recently been found, with an early diversification and less *Enterobacteriaceae* in the South [14], which thus corresponds the found North to South gradient in IBD incidence [21]. Although helminths may interact with both host innate and adoptive immunity [41] no solid data supporting the involvement of helminths in IBD aetiology has been found.

3.4. Diet

Several lines of evidence suggest that diet plays a role in IBD. Firstly, enteral nutritional therapy induces clinical and endoscopic remission [42]. The mechanism of action of enteral nutrition is unknown. It could be due to bowel rest, alteration of microbiota, and anti-inflammatory nutrients included in enteral nutrition formulae or reduced exposure to dietary risk factors. Secondly, UC and CD incidences have increased in Japan during the last 20 years. Japan has been a highly hygienic country for decades and most Japanese patients with CD lack NOD2 mutations [43]. It is possible that increase in IBD incidence is due to adoption of western diet in this population. A Japanese nationwide multicentre survey of the annual number of new patients with CD found that the increased incidence of CD was strongly correlated with increased dietary intake of total animal protein in the Japanese population [44]. As the rise in meat consumption and in IBD incidence were correlated, a causal relation was considered. The authors concluded

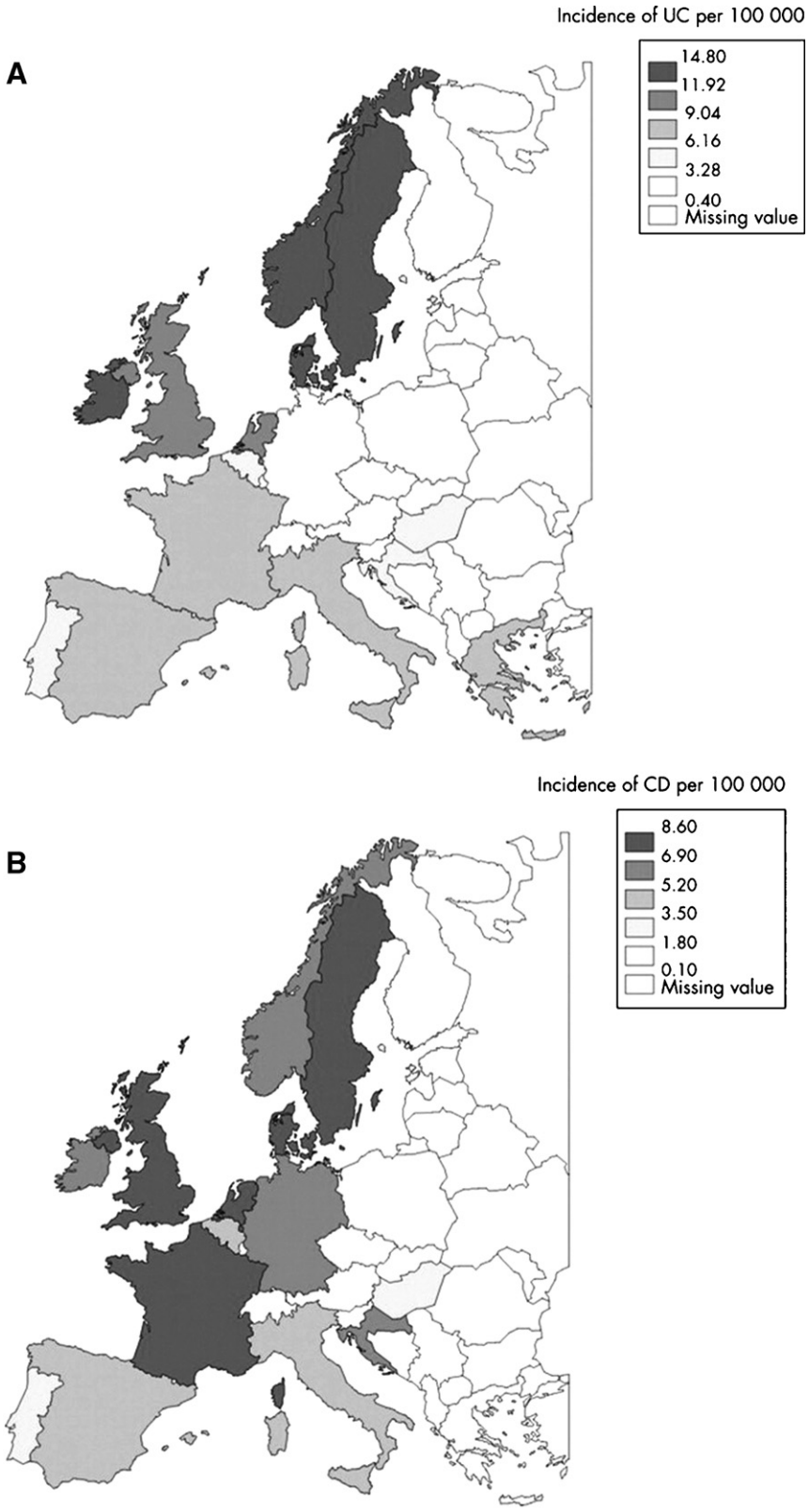

Fig. 1. Incidence of IBD across Europe. Incidence of (A) ulcerative colitis (UC) and (B) Crohn's disease (CD) [113].

that increased dietary animal protein may contribute to the development of CD [44]. Thirdly, in animal models of IBD, fatty acids, dietary fibres and phytochemicals have been found to attenuate intestinal inflammation [45].

Dietary influence has been investigated as risk factor for IBD in several different kinds of studies: observational studies, studies of dietary trends in populations and correlation with disease incidence [44,46,47] (Table 1), in retrospective case control studies

Table 1
Observational studies on dietary trends and incidence of the inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD).

Population/year	Cases	Primary observations	Main results	Ref.
Japan/1995	10,819 UC	Annual incidence of UC/1957–1985	Increase in incidence of UC parallels increase in *dairy products and meat* in Japan	[46]
Australian, Canada, USA, Europe, Japan/1988	21 countries	Incidence of CD 1970–1979; sugar and margarine consumption per capita 1962–1982	No temporal or geographical correlation between incidence of CD and *sugar and margarine* consumption	[47]
Japan/1996	n.a.[a]	Annual incidence of CD/1966–1985 Intake of dietary element in Japan 1966–1985	Correlation between incidence of CD and *animal protein*, n-6/n-3 PUFA ratio	[44]

PUFA: polyunsaturated fatty acid.
[a] Data not available.

Table 2
Prospective, population-based studies on diet and risk of the inflammatory bowel disease (IBD), ulcerative colitis (UC) and Crohn's disease (CD).

Population/year	Cohort *N*	Age at inclusion Years	Follow up Years	Incident cases $N_{IBD/UC/CD}$	Ref.
Europe[c]/2008	260,686[e]	20–80[d]	n.a.[g]	139/139/0	[52]
France/2010	67,581	40–65	10.4[b]	77/43/30[f]	[53]
Europe[c]/2009	203,193	35–74	4.0[a]	126/126/0	[54]
UK[c]/2010	25,639	46–77	4.2[a]	22/22/0	[55]

[a] Median follow-up.
[b] Mean follow-up.
[c] Part of European Prospective Investigation into Cancer and Nutrition (EPIC).
[d] Most centres recruited middle-aged volunteers.
[e] Two cohorts out of 9 were not population-based (in total 57,493 cohort members); 17 cases of UC were from these 2 cohorts.
[f] Four indeterminate IBD cases.
[g] Not available.

Table 3
Selected results from prospective, population-based studies on diet and risk of inflammatory bowel diseases.

Population/year	Main results	Risk OR (95%CI, *p*-value)[f]	Ref.
Energy intake			
Europe/2008	Energy intake	1.06 (0.89–1.26, 0.52)	[52]
Protein			
Europe/2008	Protein (% of total energy)	0.88 (0.74–1.06, 0.20)	[52]
France/2010	Total protein	3.31 (1.41–7.77, 0.007)	[53]
France/2010	Animal protein	3.03 (1.45–6.34, 0.005)	[53]
France/2010	Vegetable protein	0.88 (0.74–1.06, 0.20)	[53]
France/2010	Meat	1.87 (1.00–3.49, 0.02)	[53]
France/2010	Fish/sea products	1.83 (1.00–3.36, 0.05)	[53]
Carbohydrate			
Europe/2008	Carbohydrate (% of total energy)	1.12 (0.92–1.33, 0.26)	[52]
France/2010	Carbohydrate	0.68 (0.37–1.27, 0.26)	[53]
Fat			
Europe/2008	Fat (% of total energy)	0.99 (0.82–1.18, 0.88)	[52]
France/2010	Fat	1.24 (0.57–2.72, 0.77)	[53]
Europe/2008	MUFA[a] (% of total energy)	1.06 (0.85–1.31, 0.62)	[52]
Europe/2008	Total PUFA[b]	1.19 (0.99–1.43, 0.07)	[52]
Europe/2009	Linoleic acid[e]	1.32 (1.04–1.66, 0.02)	[54]
UK/2010	n-3 PUFA	0.56 (0.28–1.13, 0.10)	[55]
UK/2010	DHA[d]	0.43 (0.22–0.86, 0.02)	[55]
Europe/2009	DHA	0.59 (0.37–0.94, 0.03)	[54]
UK/2010	EPA[c]	0.53 (0.27–1.03, 0.06)	[55]
Europe/2009	EPA	1.37 (0.88–2.15, 0.16)	[54]
Vitamins			
Europe/2008	Vitamin C	0.92 (0.76–1.10, 0.35)	[52]
Europe/2008	Vitamin D	0.94 (0.75–1.20, 0.65)	[52]
Europe/2008	Vitamin E	1.09 (0.87–1.36, 0.45)	[52]
Europe/2008	Carotene	1.03 (0.84–1.25, 0.79)	[52]
Europe/2008	Retinol	0.93 (0.75–1.14, 0.47)	[52]

[a] Monounsaturated fatty acid.
[b] Polyunsaturated fatty acid.
[c] Eicosapentaenoic acid.
[d] Docosahexaenoic acid.
[e] Linoleic acid is a n-6 PUFA.
[f] Trend odds ratio (OR) (95% confidence interval (95%CI), *p*-value).

[48–51] (supplementary table), and in prospective cohorts [52–55] (Tables 2 and 3).

3.4.1. Meat

Meat intake in relation to risk of IBD has been included in a few retrospective case–control studies [48,51]. In a recent case–control study of 83 newly diagnosed cases of IBD, the authors reported that high consumption of red and processed meat was associated with risk of CD and UC [48]. However, only the association between CD and intake of processed meat was statistically significant with an OR of 7.80 (95%CI: 1.61–37.9) for the second vs the first tertile, whereas there was no increased association for the third and first tertiles [48], indicating that the result may be due to chance. In a retrospective case–control study of dietary patterns and risk of CD in 149 cases and 251 controls, a pattern characterized by meat, fatty foods, and desserts was positively associated with risk of CD in girls (OR = 4.7, 95%CI: 1.6–14.2) [51].

Two prospective studies have assessed diet composition in relation with subsequent development of IBD. In a large French prospective study of 67,581 middle-aged women with a mean-time follow-up of 10.4 years, 77 cases of IBD developed [53]. High total protein intake, specifically animal protein, was associated with risk of IBD [53]. Regarding sources of animal protein, high consumption of meat and fish but not of eggs or dairy products was associated with IBD risk (Hazards ratio of the third vs the first tertile was 1.87 (95%CI: 1.00–3.49, p-value = 0.02)) [53]. A prospective study that included some centres from a European multinational prospective population-based cohort study of 260,686 participants (European Prospective Investigation into Cancer and Nutrition (EPIC)) failed to find any association between any type of macronutrient and UC risk. However, there were several differences between that study and the French study. The EPIC study had a nested case–control design and included both men and women. Furthermore, in the EPIC study, intake of protein was considered as percentage of total energy including alcohol whereas in the French study, intake of macronutrients, was adjusted for energy intake using the energy partition method, considering energy from carbohydrates, from lipids, and from proteins as three separate mutually adjusted variables. How much these features would explain the different findings are under investigation [52].

In a prospective cohort study of 191 UC patients in remission, intake of meat, particularly red and processed meat, protein, and alcohol were associated with risk of relapse [56]. This study suggests that consumption of meat may aggravate the course of IBD.

3.4.2. Fish

Retrospective recall studies (supplementary table) found that eating fish protects against IBD [48,50]. In children with newly diagnosed CD, risk associated with the stated fish consumption 1 year prior to diagnosis of CD was low (OR for the fourth vs first tertile was 0.46 (95%CI: 0.20–1.06, p-value for trend = 0.02)) [50].

An increased risk was found by intake of fish or sea products in the French prospective IBD study [53] (Tables 2 and 3). On the contrary, a marginally positive association was found between total polyunsaturated fatty acid (PUFA), including n-3 and n-6 PUFA at baseline, and risk of developing IBD (Hazards ratio for the third vs first tertile of 1.87 (95%CI: 1.00–3.36, p-value = 0.05)) [53].

3.4.3. Cereals

Cereals, fruits and vegetables are sources of dietary fibres. Moreover, dietary supplements like probiotics and prebiotics confer fibres to the diet. Soluble dietary fibre is defined as the edible parts of plant foods that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine, whereas non-soluble dietary fibres are not fermented and have bulking action. Fibres are not a homogeneous entity, and their physiologic effects depend on several factors, which include its origin or sources.

Fibres impact intestinal homeostasis by several mechanisms. Fibres are fermented by bacteria in colon and give rise to the short chain fatty acids (SCFA); acetate, butyrate and propionate. Butyrate has potentially important functions in the intestine as fuel and as anti-inflammatory mediator. Thus, butyrate is the most important source of energy for intestinal enterocytes. Butyrate reduces mucosal inflammation by lowering Nuclear Factor-kappa-B (NFκB) activity in colon cells [57], and increasing apoptosis in colon cancer cells [58] and in vitro [59]. Second, high-fibre diet, probiotics, and prebiotics have been shown to manipulate the balance of beneficial and detrimental bacterial species and thereby determine homeostasis vs inflammation [60]. Moreover, an in vitro study suggests that plant fibres may affect the translocation of microbes across gut mucosa [61]. Translocation of mucosa-associated *E. coli* isolates from CD patients and from non-Crohn's controls across M-cells and Peyer's patches in monolayer culture was inhibited by the presence of certain soluble plant fibres [61]. This finding may be relevant as impairment of the intestinal barrier is considered to be a pathologic factor in IBD [62].

Cereals, and fruits and vegetables also contain various phytochemicals, such as lignans, flavonoids, and anti-oxidants, which may potentially affect inflammation. Lignans are converted by the intestinal microflora to enterolactone and enterodiol, which are weak oestrogen receptor agonists and affect various growth factors [63]. Flavonoids seem to be involved in maintenance of the intercellular tight junctions, which is one of the major determinant of the intestinal barrier function [64], the impairment of which has been associated with IBD [62]. Anti-oxidant compounds may confer some protection against inflammation [65]. The level of enterolactone in blood may be used as biomarkers for dietary intake of fibres, however, no studies on the role of enterolactone in IBD were found.

High-fibre diet has been found to attenuate experimental colitis in animal models [66] and showed benefit in active IBD [67]. High dietary fibre intake probably protects against CRC [68,69]. Intake of fruit and vegetable has been found to be inversely correlated to markers of inflammation (C-reactive protein, Interleukin-6, Tumour necrosis factor) [70]. Therefore fibres may theoretically be expected to protect against the development of IBD. However, a large prospective cohort study 260,686 participants (EPIC) found no protective effect against UC of a high intake of dietary fibres [52]. The results of retrospective studies on the relation between consumption of fibres and risk of IBD have been conflicting (supplementary table). No prospective studies were found on intake of fruit and risk of IBD. In general, retrospective studies have found a protective effect of fruits and vegetables against IBD (supplementary table).

3.4.4. Sugar

Retrospective studies have shown various relations between sugar intake and risk of IBD (supplementary table). A large prospective cohort study on 260,686 participants (EPIC) found no association between UC and intake of sugar at baseline [52]. It has hypothesized that excessive intake of highly fermentable but poorly absorbed short-chain carbohydrates and polyols may lead to bacterial overgrowth and next to increased intestinal permeability, which may confer risk of CD in genetically susceptible subjects [71]. However, support of this hypothesis in the form of, e.g. increased intestinal permeability following intake of short-chain carbohydrates is lacking.

3.4.5. Total energy

Retrospective studies have shown various relations between total protein or fat intake and the risk of IBD (supplementary table). The large French prospective study found high protein intake to be

associated with IBD (Hazards ratio for the third vs first tertile of 3.31 (95%CI: 1.41–7.77, p-value = 0.007)), specifically, animal protein (Hazards ratio for the third vs first tertile of 3.03 (95%CI: 1.45–6.34, p-value = 0.005)) [53]. However, a large prospective cohort study on 260,686 participants (EPIC) found no association between UC and macronutrient intake [52]. Thus intake of total energy, protein, fat, carbohydrate and alcohol at baseline was not associated with risk of UC [52].

3.4.6. Dietary pattern

Diet may be a proxy for a certain dietary pattern or other lifestyle factors. E.g. intake of meat may be a proxy for a high fat diet. In accordance with this view, risk may be associated with certain dietary patterns and single-nutrient analyses may be confounded by the effect of dietary patterns. To overcome such limitations, various dietary patterns have been assessed in a few studies [48,51,72]. Retrospective studies in adults found that a diet rich in white meat, fish, eggs, and potatoes was associated with low risk of UC and CD (OR for the third vs first tertile of 0.15 (95%CI: 0.04–0.51) and 0.13 (95%CI: 0.03–0.51) [48], respectively), whereas bread, butter, margarine, cheese, and meat was associated with high risk of UC (OR = 2.1, p = 0.04) [72]. In children with newly diagnosed CD, pre-disease intake of meat, fatty food, and desserts was associated with high and vegetables with low risk of CD (OR for the third vs first tertile = 4.7 (95%CI: 1.6–14.2, p = 0.006) and 0.3 (95%CI: 0.1–0.9, p = 0.029), respectively) in girls whereas intake of grains and nuts was associated with low risk of CD in boys (OR for the third vs first tertile = 0.2 (95%CI: 0.1–0.5, $p < 0.001$)) [51]. All these studies were small, retrospective studies encumbered with methodological problems.

3.4.7. Vitamins

Vitamin D ($1,25(OH)_2D$) promotes innate immunity by stimulating synthesis of the anti-microbial proteins, cathelicidin [73–75] and some defensins [76]. These antimicrobial peptides are molecules of the innate immune system located at epithelial surface in the gastrointestinal tract with anti-bacterial, antiviral and anti-fungal effect as well as chemotaxis, and cytokine and chemokine functions [76]. Thus, they protect the host from microbial growth and inflammation. Expression of cathelicidin antimicrobial peptide (CAMP) has been found to be higher in colonic tissue (inflamed and non-inflamed) from UC patients, but not in CD compared to normal individuals [77]. Similarly, other studies have suggested an impaired induction of beta defensins and cathelicidin in CD [78]. The observations support the hypothesis that a key function of vitamin D is to enhance immunity through intestinal production of antimicrobial factors.

Vitamin A has been suggested to be important for the protection against intestinal pathogens [79]. Microbial and dietary antigens activate Toll-like receptors on the surface of the intestinal cells which next initiate the innate immune response, i.e. dendritic cells (DC) leave the gut and head for the mesenteric lymph node where they induce B and T cell activation [9]. In the presence of the vitamin A metabolite retinoic acid, DC induce regulatory T cells, whereas in the absence of retinoic acid, DC induce Th17 cells leading to an inflammatory IL-17 response [80]. Furthermore, retinoic acid is involved in the correct translocation of antigen-presenting B and T cells to the gut. Retinoic acid was found to be necessary for the expression of surface markers (such as $\alpha_E\beta_7$ and CCR9) essential for the correct homing of the cells to the gut [79]. Indeed, impaired migration of B and T cells to the gut has been found in vitamin A deficient rats [79].

The higher incidence of CD observed in northern countries and regions may be due to lower sunlight exposure and resulting vitamin D deficiency, as suggested by a recent study performed in France [81]. However, no associations between dietary intake of vitamin C, D, E, Carotene, or Retinol (vitamin K) intake and later development of UC were found in a prospective European study [52]. A randomized study has shown that vitamin D supplementation reduces the risk of subsequent relapse in patients with established CD [82].

3.4.8. Food microparticles

Foodstuffs in developed countries contain increasing quantities of microparticles such as titanium dioxide and aluminium silicate. It has been suggested that microparticles act like antigen transporters from the lumen to the intestinal mucosa. In vitro, complexes formed by antigens and microparticles are powerful stimuli of T lymphocytes and macrophages [83]. One study failed to observe any difference between CD patients and controls with regard to the quantity of food microparticles contained in diet [84]. However, the role of microparticles is extremely difficult to analyse *via* a dietary questionnaire. A therapeutic trial including 18 corticosteroid-dependant patients, randomized to receive a normal and a microparticle-reduced diet concluded to the efficacy of the latter [85]. This was not confirmed in a subsequent multicentre trial [86].

4. Discussion

Prospective studies suggest that a diet high in protein, particular animal protein, may be associated with risk of IBD and risk of relapse [56,53]. Also, a diet high in n-3 PUFA may protect from and a diet high in n-6 PUFAs may predispose to UC [52,54], whereas no effects of fibres, sugar and total energy intake on risk of UC were found in a prospective study [52]. Regarding other food items, data are even more scarce.

In spite of the few data supporting a role of individual food items in the development of IBD, some data support an important role of diet in treatment of IBD [56]. Thus, in the paediatric population, exclusive enteral nutrition may be equivalent to corticosteroids in inducing remission in acute CD [17] suggesting a major effect of diet on intestinal inflammation.

How may intake of diet affect risk of IBD? Dietary components may affect gut homeostasis directly by affecting oxidative stress [87], by affecting the expression of transcription factors involved in the regulation of intestinal inflammation [88,89], and by affecting mediators involved in the inflammatory response such as short-chain fatty acids [12,90]. Additionally, diet may affect inflammation indirectly *via* impact on gut microbiota [13,14] and, although the gut microbiota has been considered to be stable in the individual over time [14], new studies suggest that the gut ecosystem is less stable than previously thought. Meat is the main source of haem. Haem is degraded to carbon monoxide (CO), iron, and bilirubin. Haem and iron may promote inflammation by generation of reactive oxygen species [91] whilst, on the other hand, bilirubin and CO have been shown to reduce cellular oxidative stress and inhibit pro-inflammatory cytokines. In particular, iron potentiated colitis in IL-10 knock-out mice [92]. Also, iron is a key regulator of host–pathogen interactions [93] and the concentration of iron in drinking water has been associated with risk of IBD [94]. The expected effect of dietary intake of haem is therefore obscure. Certain functional variants in the gene coding for haem oxygenase-1 result in low haem degradation activity [95]. Thus, carriers of the "low activity" variants should be at high risk of IBD in case of haem, bilirubin or CO being important for IBD development, or, on the contrary, low risk in case of iron being an important risk factor. However, we did not find any association between the functional haem oxygenase-1 polymorphisms and risk of UC or CD, which does exclude that haem or haem iron play a significant role in development of IBD [95].

Meat also represents sources of heterocyclic amines, polycyclic aromatic hydrocarbons (PAH) and N-nitroso compounds which are carcinogens caused by cooking at high temperature and by processing of meat [96]. Also cereals, as well as tobacco smoking, are sources of PAH and their overall contribution to dietary PAH is higher than meat, particularly in the northern Europe [68]. Therefore, in case of PAH being a substantial risk factor, these items could be expected to also be associated with risk of IBD. Unfortunately, knowledge on potential associations is scarce.

In addition, meat is a source of n-6 PUFA, including arachidonic acid (AA). High levels of AA have been found in the colon mucosa of IBD patients when compared with healthy subjects [97]. In an Il10−/− mice model of IBD, dietary AA decreased the expression levels of some colonic genes in the oxidative stress and acute phase response pathways compared with mice fed an oleic acid diet [98]. The authors suggested that dietary AA, in the applied experimental conditions, is not pro-inflammatory, but, on the contrary, protects colonocytes from oxidative stress in the Il10−/− mice [98]. Interestingly, a European multinational prospective population-based cohort study of 260,686 participants (EPIC) found that baseline intake of the n-6 PUFA, linoleic acid, was associated with risk of developing UC, showing a significant trend over quartiles [54]. Linoleic acid is the primary dietary n-6 PUFA, constituting 85–90% of the dietary n-6 PUFA [99]. Linoleic acid is present in red meat, and certain cooking oils and margarines. Of interest, intake of margarine was significantly associated with high risk of UC in two retrospective case–control studies [48,72]. Dietary n-6 PUFAs, including linoleic acid and AA, are metabolized to pro-inflammatory eicosanoids such as prostaglandins, leukotrienes and tromboxane, whereas dietary n-3 PUFA is converted to anti-inflammatory molecules such as prostacyclins, lipoxins and epoxy-eicosatrienoic acids [99]. AA and its various metabolites may promote intestinal inflammation in principally two ways [90]. First, by the regulation of the mucosal barrier by affecting the tight junction molecules with subsequent impaired paracellular permeability and, second, by the regulation of the inflammatory response leading to high levels of cytokines, eicosanoids and free radicals [90]. Moreover, the intestinal homeostasis is maintained by commensal microbials by the regulation of, e.g. NFκB signalling and the activation of peroxisome proliferator-activated receptor (PPAR) which results in down-regulation of the cyclooxygenase-2 (COX-2) enzyme activity and AA cascade [90]. Whereas the intestinal production of AA and its various metabolites are controlled by immune cells and enterocytes [90], it has been recognized that dietary fatty acids may affect intestinal inflammation [100]. The prospective study suggested that AA in the diet may be associated with an increased risk of IBD development [54]. Analyses of fatty acid composition of adipose tissue (which reflects dietary intake) showed that high level of AA at baseline was associated with a 4-fold increased risk of developing UC [100]. Furthermore, a statistically significant dose-response effect was found which supports a causal association.

Moreover, another mechanism may be suggested. Meat may vehicle bacteria that play a role in the pathogenesis of CD. According to the cold chain hypothesis, CD could be caused by *Yersinia* species which, in NOD2-mutated patients lead to permanent activation of NFκB [81]. Meat contains huge amounts of *Yersinia*. Finally, theoretically, antibiotics used in the production of meat such as pork may still be present in the prepared food and affect intestinal microflora and thereby intestinal homeostasis [101].

Fish are sources of n-3 PUFA. A prospective cohort study of 22 incident cases of UC found a non-significant protective effect of baseline intake of n-3 PUFAs and later development of UC [55] (OR for the third vs first tertile of 0.54 (95%CI: 0.27–1.05, p-value = 0.07)) (Table 2). However, the prospective studies were based on only 43 and 22 UC cases, respectively [53,55]. A potential anti-inflammatory effect of n-3 PUFA in relation to risk of diseases which involve inflammation is suggested by studies indicating that high n-3 PUFA tissue levels does reduce the risk for cardiovascular disease risk [102].

How could diet differently influence the development of CD and UC? The recent year's genetic studies have promoted the understanding of disease pathogenesis. Whereas some pathways involving intestinal immune homeostasis seem to be common to both CD and UC, e.g. IL10 signalling [95], CD is characterized by defective processing of intracellular bacteria and UC is characterized by disorders in epithelial barrier function [103]. Moreover, the found low concordance rate in genetically identical twins, in particular in UC twins, suggests that the fraction of the aetiology caused by environmental factors is larger for UC than for CD [19,28,29]. Also, the incidence of UC seemed to increase rapidly in relation to urbanization, whilst the number of patients with CD remained low or seemed to increase with a delay of approximately 15 years compared to UC [25]. Importantly, the changing pattern could not be explained by changes in smoking habits, a major risk factor of IBD [21,25]. Thus, changes in life-style factors seem to affect UC risk, reflected in increased incidence, years before CD risk is affected. Although not proven, diet may be involved. Taken together, it is suggests that different food items may affect CD and UC development differently.

Genetic susceptibility coupled with gene-environment interaction with certain food items may contribute to IBD risk [12]. First, disease distribution and phenotypic appearance differ significantly between ethnic groups and even within populations [104]. Second, emerging evidence suggests that the contribution from each gene to IBD development may vary considerably amongst different populations. A remarkable amount of heterogeneity across ethnicities and populations has been found for IBD risk candidate genes such as *NOD2* [105,106], *COX-2* [103], and *ABCB1* (*MDR1*) [107,108] gene variants. Varying diet-gene interactions may contribute to these results.

The strengths and limitations of the study designs have to be taken into account. In general, in observational studies, a causal relationship between the observed parameters can be suggested, but not proved. Moreover, only few studies take smoking status into account even though smoking has high impact on risk of IBD [30]. Smoking is also known to be related to dietary habits [109] indicating that smoking may be an important confounding factor.

In trend studies, correlations between intake of one or more dietary items in the population and disease incidence have been studied. These studies are encumbered with methodological problems. First, the intake of the investigated food item by the individual subjects is not considered, thus, the distribution of the disease and the food items may not be associated. Next, the temporal relationship between the exposure and the disease is not accounted for [44,47].

Case–control studies are encumbered with methodological problems. Recall failure may be prominent in IBD because disease manifestations such as weight loss and abdominal pain may have changed the diet prior to the diagnosis. This topic has been critically reviewed and it was concluded that reported positive associations were likely a reflection of post-illness and not pre-illness consumption [110]. To overcome this disadvantage, therefore, some studies have interviewed the patients about pre-illness dietary habits, at time of the diagnosis [48].

Prospective studies have the advantage that they are not biassed by recalling failure with respect to diet. On the other hand, prospective studies are more tedious and strenuous and generally include much fewer IBD patients than case–control studies. In the recent years, prospective populations-based studies on diet and subsequent development of IBD with long observational periods have appeared [52–55]. As these studies were designed to explore the

relation of diet and cancer development, age of the included persons were, in general, above the age, where the incidence of IBD is highest [53]. Therefore, generalizations of the findings to those of younger age may not be appropriate. Also, whereas publication bias may particularly affect the publication of case–control and trend studies with negative results, this bias is expected to have less effect on the publication of prospective studies.

Meat is an appealing candidate for further studies on diet in relation to IBD. Northern European countries, including Denmark, are characterized by (1) a high meat intake [111], (2) high incidences of IBD, and (3) low frequencies of NOD2 mutations [105].

5. Conclusion

Methodological problems may contribute to the various results found by the retrospective studies.

Prospective studies suggest that a diet high in protein, particular animal protein, may be associated with risk of IBD and risk of relapse and n-6 PUFAs may predispose to UC whilst a diet high in n-3 PUFA may protect from UC. However, no food item reaches the causality criteria's described by Austin Bradford Hill [112]. Some studies found an association between one food item and subsequent IBD but these findings were not reproduced. More data may be expected during the coming years due to the ongoing observation of existing populations-based cohorts.

Conflict of interest

None declared.

List of abbreviations

95%CI, 95% confidence interval; AA, arachidonic acid; CD, Crohn's disease; CO, carbon monoxide; COX-2, cyclooxygenase-2; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; EPIC, European Prospective Investigation into Cancer and Nutrition; HCA, heterocyclic amines; IBD, inflammatory bowel disease; MUFA, monounsaturated fatty acid; n.a., data not available; NFκB, Nuclear Factor-kappa-B; OR, odds ratio; PAH, polycyclic aromatic hydrocarbons; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RR, relative risk; SCFA, short chain fatty acids; UC, ulcerative colitis.

Acknowledgements

We thank the staff at the Information Department and Library, Viborg Regional Hospital, for valuable help.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.dld.2011.10.001.

References

[1] Baumgart DC, Carding SR. Inflammatory bowel disease: cause and immunobiology. Lancet 2007;369:1627–40.
[2] Kalischuk LD, Buret AG. A role for *Campylobacter jejuni*-induced enteritis in inflammatory bowel disease? Am J Physiol Gastrointest Liver Physiol 2010;298:G1–9.
[3] Kappelman MD, Rifas-Shiman SL, Porter CQ, et al. Direct health care costs of Crohn's disease and ulcerative colitis in US children and adults. Gastroenterology 2008;135:1907–13.
[4] Odes S, Vardi H, Friger M, et al. Cost analysis and cost determinants in a European inflammatory bowel disease inception cohort with 10 years of follow-up evaluation. Gastroenterology 2006;131:719–28.
[5] Strober W, Fuss I, Mannon P. The fundamental basis of inflammatory bowel disease. J Clin Invest 2007;117:514–21.
[6] Anderson CA, Massey DC, Barrett JC, et al. Investigation of Crohn's disease risk loci in ulcerative colitis further defines their molecular relationship. Gastroenterology 2009;136:523–9.
[7] Franke A, McGovern DP, Barrett JC, et al. Genome-wide meta-analysis increases to 71 the number of confirmed Crohn's disease susceptibility loci. Nat Genet 2010;42:1118–25.
[8] Fukata M, Abreu MT. Pathogen recognition receptors, cancer and inflammation in the gut. Curr Opin Pharmacol 2009;9:680–7.
[9] Fukata M, Vamadevan AS, Abreu MT. Toll-like receptors (TLRs) and Nod-like receptors (NLRs) in inflammatory disorders. Semin Immunol 2009;21:242–53.
[10] Xavier RJ, Podolsky DK. Unravelling the pathogenesis of inflammatory bowel disease. Nature 2007;448:427–34.
[11] Bosscher D, Breynaert A, Pieters L, et al. Food-based strategies to modulate the composition of the intestinal microbiota and their associated health effects. J Physiol Pharmacol 2009;60(Suppl. 6):5–11.
[12] Ferguson LR. Nutrigenomics and inflammatory bowel diseases. Expert Rev Clin Immunol 2010;6:573–83.
[13] Neish AS. Microbes in gastrointestinal health and disease. Gastroenterology 2009;136:65–80.
[14] Dore J, Corthier G. The human intestinal microbiota. Gastroenterol Clin Biol 2010;34(Suppl. 1):S7–15.
[15] Flint HJ, Duncan SH, Scott KP, et al. Interactions and competition within the microbial community of the human colon: links between diet and health. Environ Microbiol 2007;9:1101–11.
[16] Lakatos PL. Environmental factors affecting inflammatory bowel disease: have we made progress? Dig Dis 2009;27:215–25.
[17] Buchanan E, Gaunt WW, Cardigan T, et al. The use of exclusive enteral nutrition for induction of remission in children with Crohn's disease demonstrates that disease phenotype does not influence clinical remission. Aliment Pharmacol Ther 2009;30:501–7.
[18] Lakatos PL. Recent trends in the epidemiology of inflammatory bowel diseases: up or down? World J Gastroenterol 2006;12:6102–8.
[19] Loftus Jr EV. Clinical epidemiology of inflammatory bowel disease: Incidence, prevalence, and environmental influences. Gastroenterology 2004;126:1504–17.
[20] Economou M, Pappas G. New global map of Crohn's disease: genetic, environmental, and socioeconomic correlations. Inflamm Bowel Dis 2008;14:709–20.
[21] Shivananda S, Lennard-Jones J, Logan R, et al. Incidence of inflammatory bowel disease across Europe: is there a difference between north and south? Results of the European Collaborative Study on Inflammatory Bowel Disease (EC-IBD). Gut 1996;39:690–7.
[22] Armitage EL, Aldhous MC, Anderson N, et al. Incidence of juvenile-onset Crohn's disease in Scotland: association with northern latitude and affluence. Gastroenterology 2004;127:1051–7.
[23] Kappelman MD, Rifas-Shiman SL, Kleinman K, et al. The prevalence and geographic distribution of Crohn's disease and ulcerative colitis in the United States. Clin Gastroenterol Hepatol 2007;5:1424–9.
[24] Nerich V, Monnet E, Etienne A, et al. Geographical variations of inflammatory bowel disease in France: a study based on national health insurance data. Inflamm Bowel Dis 2006;12:218–26.
[25] Logan I, Bowlus CL. The geoepidemiology of autoimmune intestinal diseases. Autoimmun Rev 2009;9:A372–8.
[26] Noble CL, Arnott ID. What is the risk that a child will develop inflammatory bowel disease if 1 or both parents have IBD? Inflamm Bowel Dis 2008;14(Suppl. 2):S22–3.
[27] Halfvarson J, Jess T, Magnuson A, et al. Environmental factors in inflammatory bowel disease: a co-twin control study of a Swedish–Danish twin population. Inflamm Bowel Dis 2006;12:925–33.
[28] Halme L, Paavola-Sakki P, Turunen U, et al. Family and twin studies in inflammatory bowel disease. World J Gastroenterol 2006;12:3668–72.
[29] Marshall JK. Are there epidemiological differences between Crohn's disease and ulcerative colitis? Inflamm Bowel Dis 2008;14(Suppl. 2):S1.
[30] Mahid SS, Minor KS, Soto RE, et al. Smoking and inflammatory bowel disease: a meta-analysis. Mayo Clin Proc 2006;81:1462–71.
[31] Gearry RB, Richardson AK, Frampton CM, et al. Population-based cases control study of inflammatory bowel disease risk factors. J Gastroenterol Hepatol 2010;25:325–33.
[32] Frisch M, Pedersen BV, Andersson RE. Appendicitis, mesenteric lymphadenitis, and subsequent risk of ulcerative colitis: cohort studies in Sweden and Denmark. Br Med J 2009;338:b716, doi:10.1136/bmj.b716.
[33] Hviid A, Svanstrom H, Frisch M. Antibiotic use and inflammatory bowel diseases in childhood. Gut 2011;60:49–54.
[34] Kaplan GG, Jackson T, Sands BE, et al. The risk of developing Crohn's disease after an appendectomy: a meta-analysis. Am J Gastroenterol 2008;103:2925–31.
[35] Gradel KO, Nielsen HL, Schonheyder HC, et al. Increased short- and long-term risk of inflammatory bowel disease after salmonella or campylobacter gastroenteritis. Gastroenterology 2009;137:495–501.

[36] Jess T, Simonsen J, Nielsen NM, et al. Enteric Salmonella or Campylobacter infections and the risk of inflammatory bowel disease. Gut 2011;60:318–24.
[37] Marchesi JR. Prokaryotic and eukaryotic diversity of the human gut. Adv Appl Microbiol 2010;72:43–62.
[38] Marteau P. Bacterial flora in inflammatory bowel disease. Dig Dis 2009;27(Suppl. 1):99–103.
[39] Nell S, Suerbaum S, Josenhans C. The impact of the microbiota on the pathogenesis of IBD: lessons from mouse infection models. Nat Rev Microbiol 2010;8:564–77.
[40] Round JL, Mazmanian SK. Inducible Foxp3+ regulatory T-cell development by a commensal bacterium of the intestinal microbiota. Proc Natl Acad Sci USA 2010;107:12204–9.
[41] Weinstock JV, Elliott DE. Helminths and the IBD hygiene hypothesis. Inflamm Bowel Dis 2009;15:128–33.
[42] Zachos M, Tondeur M, Griffiths AM. Enteral nutritional therapy for induction of remission in Crohn's disease. Cochrane Database Syst Rev 2007;1:CD000542.
[43] Inoue N, Tamura K, Kinouchi Y, et al. Lack of common NOD2 variants in Japanese patients with Crohn's disease. Gastroenterology 2002;123: 86–91.
[44] Shoda R, Matsueda K, Yamato S, et al. Epidemiologic analysis of Crohn disease in Japan: increased dietary intake of n-6 polyunsaturated fatty acids and animal protein relates to the increased incidence of Crohn disease in Japan. Am J Clin Nutr 1996;63:741–5.
[45] Hakansson A, Branning C, Adawi D, et al. Blueberry husks, rye bran and multistrain probiotics affect the severity of colitis induced by dextran sulphate sodium. Scand J Gastroenterol 2009;44:1213–25.
[46] Kitahora T, Utsunomiya T, Yokota A. Epidemiological study of ulcerative colitis in Japan: incidence and familial occurrence. The Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. J Gastroenterol 1995;30(Suppl. 8):5–8.
[47] Sonnenberg A. Geographic and temporal variations of sugar and margarine consumption in relation to Crohn's disease. Digestion 1988;41:161–71.
[48] Maconi G, Ardizzone S, Cucino C, et al. Pre-illness changes in dietary habits and diet as a risk factor for inflammatory bowel disease: a case–control study. World J Gastroenterol 2010;16:4297–304.
[49] Sakamoto N, Kono S, Wakai K, et al. Dietary risk factors for inflammatory bowel disease: a multicenter case–control study in Japan. Inflamm Bowel Dis 2005;11:154–63.
[50] Amre DK, D'Souza S, Morgan K, et al. Imbalances in dietary consumption of fatty acids, vegetables, and fruits are associated with risk for Crohn's disease in children. Am J Gastroenterol 2007;102:2016–25.
[51] D'Souza S, Levy E, Mack D, et al. Dietary patterns and risk for Crohn's disease in children. Inflamm Bowel Dis 2008;14:367–73.
[52] Hart AR, Luben R, Olsen A, et al. Diet in the aetiology of ulcerative colitis: a European prospective cohort study. Digestion 2008;77:57–64.
[53] Jantchou P, Morois S, Clavel-Chapelon F, et al. Animal protein intake and risk of inflammatory bowel disease: the E3N prospective study. Am J Gastroenterol 2010;105:2195–201.
[54] Tjonneland A, Overvad K, Bergmann MM, et al. Linoleic acid, a dietary n-6 polyunsaturated fatty acid, and the aetiology of ulcerative colitis: a nested case–control study within a European prospective cohort study. Gut 2009;58:1606–11.
[55] John S, Luben R, Shrestha SS, et al. Dietary n-3 polyunsaturated fatty acids and the aetiology of ulcerative colitis: a UK prospective cohort study. Eur J Gastroenterol Hepatol 2010;22:602–6.
[56] Jowett SL, Seal CJ, Pearce MS, et al. Influence of dietary factors on the clinical course of ulcerative colitis: a prospective cohort study. Gut 2004;53:1479–84.
[57] Luhrs H, Gerke T, Muller JG, et al. Butyrate inhibits NF-kappaB activation in lamina propria macrophages of patients with ulcerative colitis. Scand J Gastroenterol 2002;37:458–66.
[58] Pajak B, Orzechowski A, Gajkowska B. Molecular basis of sodium butyrate-dependent proapoptotic activity in cancer cells. Adv Med Sci 2007;52: 83–8.
[59] Tedelind S, Westberg F, Kjerrulf M, et al. Anti-inflammatory properties of the short-chain fatty acids acetate and propionate: a study with relevance to inflammatory bowel disease. World J Gastroenterol 2007;13:2826–32.
[60] Damaskos D, Kolios G. Probiotics and prebiotics in inflammatory bowel disease: microflora 'on the scope'. Br J Clin Pharmacol 2008;65:453–67.
[61] Roberts CL, Keita AV, Duncan SH, et al. Translocation of Crohn's disease *Escherichia coli* across M-cells: contrasting effects of soluble plant fibres and emulsifiers. Gut 2010;59:1331–9.
[62] Meddings J. The significance of the gut barrier in disease. Gut 2008;57:438–40.
[63] Adlercreutz H. Lignans and human health. Crit Rev Clin Lab Sci 2007;44:483–525.
[64] Suzuki T, Hara H. Role of flavonoids in intestinal tight junction regulation. J Nutr Biochem 2010.
[65] Eberlein M, Scheibner KA, Black KE, et al. Anti-oxidant inhibition of hyaluronan fragment-induced inflammatory gene expression. J Inflamm (Lond) 2008;5:20.
[66] Schrenk D. Dietary fiber, low-molecular-weight food constituents and colo-rectal inflammation in animal models—a review. Mol Nutr Food Res 2009;53:1281–8.
[67] Yamamoto T, Nakahigashi M, Saniabadi AR. Review article: diet and inflammatory bowel disease—epidemiology and treatment. Aliment Pharmacol Ther 2009;30:99–112.
[68] World Cancer Research Fund/American Institute for Cancer Research FNPAatoCaGPA, http://www.dietandcancerreport.org/. Washington, DC; 2007.
[69] Gonzalez CA. The European Prospective Investigation into Cancer and Nutrition (EPIC). Public Health Nutr 2006;9:124–6.
[70] Holt EM, Steffen LM, Moran A, et al. Fruit and vegetable consumption and its relation to markers of inflammation and oxidative stress in adolescents. J Am Diet Assoc 2009;109:414–21.
[71] Gibson PR, Shepherd SJ. Personal view: food for thought—western lifestyle and susceptibility to Crohn's disease The FODMAP hypothesis. Aliment Pharmacol Ther 2005;21:1399–409.
[72] A case–control study of ulcerative colitis in relation to dietary and other factors in Japan. The Epidemiology Group of the Research Committee of Inflammatory Bowel Disease in Japan. J Gastroenterol 1995;30(Suppl. 8):9–12.
[73] Hewison M. Vitamin D and the immune system: new perspectives on an old theme. Endocrinol Metab Clin North Am 2010;39:365–79 [Table].
[74] Liu PT, Stenger S, Tang DH, et al. Cutting edge: vitamin D-mediated human antimicrobial activity against *Mycobacterium tuberculosis* is dependent on the induction of cathelicidin. J Immunol 2007;179:2060–3.
[75] Liu N, Kaplan AT, Low J, et al. Vitamin D induces innate antibacterial responses in human trophoblasts via an intracrine pathway. Biol Reprod 2009;80:398–406.
[76] Schwalfenberg GK. A review of the critical role of vitamin D in the functioning of the immune system and the clinical implications of vitamin D deficiency. Mol Nutr Food Res 2011;55:96–108.
[77] Schauber J, Rieger D, Weiler F, et al. Heterogeneous expression of human cathelicidin hCAP18/LL-37 in inflammatory bowel diseases. Eur J Gastroenterol Hepatol 2006;18:615–21.
[78] Wehkamp J, Schmid M, Stange EF. Defensins other antimicrobial peptides in inflammatory bowel disease. Curr Opin Gastroenterol 2007;23:370–8.
[79] Mora JR, von Andrian UH. Differentiation and homing of IgA-secreting cells. Mucosal Immunol 2008;1:96–109.
[80] Xu L, Kitani A, Stuelten C, et al. Positive and negative transcriptional regulation of the Foxp3 gene is mediated by access and binding of the Smad3 protein to enhancer I. Immunity 2010;33:313–25.
[81] Hugot JP, Alberti C, Berrebi D, et al. Crohn's disease: the cold chain hypothesis. Lancet 2003;362:2012–5.
[82] Jorgensen SP, Agnholt J, Glerup H, et al. Clinical trial: vitamin D3 treatment in Crohn's disease—a randomized double-blind placebo-controlled study. Aliment Pharmacol Ther 2010;32:377–83.
[83] Ekbom A, Montgomery SM. Environmental risk factors (excluding tobacco and microorganisms): critical analysis of old and new hypotheses. Best Pract Res Clin Gastroenterol 2004;18:497–508.
[84] Lomer MC, Hutchinson C, Volkert S, et al. Dietary sources of inorganic microparticles and their intake in healthy subjects and patients with Crohn's disease. Br J Nutr 2004;92:947–55.
[85] Lomer MC, Thompson RP, Powell JJ. Fine and ultrafine particles of the diet: influence on the mucosal immune response and association with Crohn's disease. Proc Nutr Soc 2002;61:123–30.
[86] Lomer MC, Grainger SL, Ede R, et al. Lack of efficacy of a reduced microparticle diet in a multi-centred trial of patients with active Crohn's disease. Eur J Gastroenterol Hepatol 2005;17:377–84.
[87] Kruidenier L, Verspaget HW. Review article: oxidative stress as a pathogenic factor in inflammatory bowel disease—radicals or ridiculous? Aliment Pharmacol Ther 2002;16:1997–2015.
[88] Wang K, Wan YJ. Nuclear receptors and inflammatory diseases. Exp Biol Med (Maywood) 2008;233:496–506.
[89] Langmann T, Moehle C, Mauerer R, et al. Loss of detoxification in inflammatory bowel disease: dysregulation of pregnane X receptor target genes. Gastroenterology 2004;127:26–40.
[90] Ferrer R, Moreno JJ. Role of eicosanoids on intestinal epithelial homeostasis. Biochem Pharmacol 2010;80:431–8.
[91] Joosen AM, Kuhnle GG, Aspinall SM, et al. Effect of processed and red meat on endogenous nitrosation and DNA damage. Carcinogenesis 2009;30:1402–7.
[92] Schepens MA, Vink C, Schonewille AJ, et al. Dietary heme adversely affects experimental colitis in rats, despite heat-shock protein induction. Nutrition 2011;27:590–7.
[93] Doherty CP. Host–pathogen interactions: the role of iron. J Nutr 2007;137:1341–4.
[94] Aamodt G, Bukholm G, Jahnsen J, et al. The association between water supply and inflammatory bowel disease based on a 1990–1993 cohort study in southeastern Norway. Am J Epidemiol 2008;168:1065–72.
[95] Andersen V, Ernst A, Christensen J, et al. The polymorphism rs3024505 proximal to IL-10 is associated with risk of ulcerative colitis and Crohn's disease in a Danish case–control study. BMC Med Genet 2010;11:82.
[96] Santarelli RL, Pierre F, Corpet DE. Processed meat and colorectal cancer: a review of epidemiologic and experimental evidence. Nutr Cancer 2008;60:131–44.
[97] Nishida T, Miwa H, Shigematsu A, et al. Increased arachidonic acid composition of phospholipids in colonic mucosa from patients with active ulcerative colitis. Gut 1987;28:1002–7.
[98] Knoch B, Barnett MP, McNabb WC, et al. Dietary arachidonic acid-mediated effects on colon inflammation using transcriptome analysis. Mol Nutr Food Res 2010;54(Suppl. 1):S62–74.
[99] Harris WS, Mozaffarian D, Rimm E, et al. Omega-6 fatty acids and risk for cardiovascular disease: a science advisory from the American Heart Association

Nutrition Subcommittee of the Council on Nutrition Physical Activity, and Metabolism; Council on Cardiovascular Nursing; and Council on Epidemiology and Prevention. Circulation 2009;119:902–7.
[100] de Silva PS, Olsen A, Christensen J, et al. An association between dietary arachidonic acid, measured in adipose tissue, and ulcerative colitis. Gastroenterology 2010;139:1912–7.
[101] EU Food Safety – From Farm to Fork, Residues of veterinary medicinal products – control and monitoring, http://ec.europa.eu/food/food/chemicalsafety/residues/control_en.htm; 2011.
[102] Joensen AM, Schmidt EB, Dethlefsen C, et al. Dietary intake of total marine n-3 polyunsaturated fatty acids, eicosapentaenoic acid, docosahexaenoic acid and docosapentaenoic acid and the risk of acute coronary syndrome—a cohort study. Br J Nutr 2010;103:602–7.
[103] Andersen V, Nimmo E, Krarup HB, et al. Cyclooxygenase-2 (COX-2) polymorphisms and risk of inflammatory bowel disease in a Scottish and Danish case–control study. Inflamm Bowel Dis 2011;17:937–46.
[104] Walker DG, Williams HR, Kane SP, et al. Differences in inflammatory bowel disease phenotype between South Asians and Northern Europeans living in North West London, UK. Am J Gastroenterol 2011;106:1281–9.
[105] Ernst A, Jacobsen B, Ostergaard M, et al. Mutations in CARD15 and smoking confer susceptibility to Crohn's disease in the Danish population. Scand J Gastroenterol 2007;42:1445–51.
[106] van der LK, Boor PP, Houwing-Duistermaat JJ, et al. CARD15 mutations in Dutch familial and sporadic inflammatory bowel disease and an overview of European studies. Eur J Gastroenterol Hepatol 2007;19:449–59.
[107] Ostergaard M, Ernst A, Labouriau R, et al. Cyclooxygenase-2, multidrug resistance 1, and breast cancer resistance protein gene polymorphisms and inflammatory bowel disease in the Danish population. Scand J Gastroenterol 2009;44:65–73.
[108] Annese V, Valvano MR, Palmieri O, et al. Multidrug resistance 1 gene in inflammatory bowel disease: a meta-analysis. World J Gastroenterol 2006;12:3636–44.
[109] Ma J, Betts NM, Hampl JS. Clustering of lifestyle behaviors: the relationship between cigarette smoking, alcohol consumption, and dietary intake. Am J Health Promot 2000;15:107–17.
[110] Riordan AM, Ruxton CH, Hunter JO. A review of associations between Crohn's disease and consumption of sugars. Eur J Clin Nutr 1998;52:229–38.
[111] World Resources Institute. Earth Trends, The environmental information portal, http://earthtrends.wri.org/searchable_db/index.php?theme=8&variable_ID=193&action=select_countries; 2009.
[112] Hill BA. The environment and disease: association or causation? Proc R Soc Med 1965;58:295–300.
[113] Frangos CC, Frangos CC. Inflammatory bowel disease: reviewing an old study under a new perspective. Gut 2007;56:1638–9.